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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,880	10/22/2003	Nancy M. Lee	1034516-000006	8369

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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,880	LEE ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93,96 and 97* is/are pending in the application.

4a) Of the above claim(s) *1-48,50,65-78,80 and 89-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,51-64,79,81-88,96 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/07 and 7/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 1/9/2007, 4/2/2007 and 4/30/2007 in which claims 49, 51-52, 56-57, 61, 64, 79, 81 and 84 were amended; claims 94-95 were cancelled; and claims 69-97 were added. Claims 1-93 and 96-97 are pending. Claims 1-48, 50, 65-78, 80, 89-93 are withdrawn. Claims 49, 51-64, 79, 81-88 and 96-97 are under examination in the instant Office action.

Any rejection of record not recited herein is hereby WITHDRAWN.

Election/Restrictions

This application contains claims 1-48, 50, 65-78, 80 and 89-93 drawn to an invention nonelected with traverse in the reply filed 6/21/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Oath/Declaration

Receipt is acknowledged of the substitute oath/declaration filed 1/9/2007. The substitute oath/declaration is found to be compliant with 37 C.F.R. 1.679(a).

Priority

Applicant's claim for the benefit of priority to provisional application 60/488,660, submitted 7/18/2003, is acknowledged. However, application 60/488,660 does not disclose polynucleotide sequences for any of the claimed polynucleotides or primers recited in the instant claims. Furthermore, application 60/488,660 does not disclose the use of an SAA1 gene in a biomarker panel for colorectal cancer or colorectal polyps. Therefore, priority for the claimed invention is granted only as far back as the filing date of the instant application: 10/22/2003.

Response to Arguments

Applicant argues that neither examples nor DNA sequences are required to provide adequate written description support for a claim if references contemporaneous with the filing date show relevant genes and nucleotide sequences to demonstrate knowledge to those skilled in the art. Applicant cites *Falkner v. Inglis*,

448 F.3d 1357, 79 USPQd 1001 (Fed. Cir. 2006) and argues that the position in *Falkner* is consistent with the long held position that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d, 1331, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S.947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Applicant further argues that because the gene sequences recited in the present application were known and accessible in databases at the time of the provisional filing, the provisional document supports the presently claimed invention.

Applicant's arguments have been carefully considered but are respectfully found unpersuasive. Examiner agrees with Applicant insofar as Applicant need not disclose what is well known in the art. However, Applicant's argument that because the gene sequences recited in Applicant's instant claims were known in the art at the time of filing, the provisional document necessarily supports the presently claimed invention is not persuasive because Examiner does not contend that if such

sequences were known in the prior art, the priority document need not disclose them. Instead, Examiner wishes to emphasize and to clarify that Applicant's invention is drawn *methods* for measuring polynucleotide sequences for use as biomarkers for colorectal cancer. The priority document does not provide support for such a *method, wherein the method involves the use of the recited SEQ ID numbers*. The disclosure of the claimed method is what is required for benefit of Applicant's claimed priority to provisional Appl. No. 60/488,660.

Specification

Applicant's amendment to the specification in the papers filed 1/9/2007 is acknowledged.

Claim Objections

The objection to claims 49, 51-64, 79 and 81-88 is withdrawn in view of Applicant's amendment to claims 49, 51-52, 56-57, 61, 64, 79, 81 and 84.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-59 and 96-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection. This is a new rejection necessitated by Applicant's amendment.**

The specification as originally filed does not provide support for the invention as now claimed: "[t]he method of claim 49, where the cDNA levels for the sample are compared to cDNA level from an independently validated normal control" (claim 56), or "[t]he method of claim 56, wherein an increase in at least one cDNA in the sample compared to cDNA levels from the independently validated normal control identifies the subject as a candidate for the management of colorectal cancer and colorectal polyps" (claim 57). The specification does not provide sufficient blazemarks or direction for the instant controls encompassed by the above-mentioned limitation, as currently recited. Neither does the specification provide

sufficient blazemarks nor direction for the instant limitation wherein an increase in at least one recited cDNA compared to a validated control (of any kind) identifies the subject as a candidate for the management of colorectal cancer and colorectal polyps. The instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 49, 51-64, 79, 81-88 and 96-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record and extended to new claims 96-97.**

Response to Arguments

Applicant argues that gene expression profiling for patient care is common in the art. Applicant further argues that "controls" are routinely used in the art of nucleic acid analysis and refers Examiner to the amended claims. Applicant further argues that the specification teaches that AFP and CEA biomarkers have been used for over four decades and that biomarkers have five potential uses in the management of patient care: "risk assessment, early diagnosis, establishing prognosis, monitoring treatment and detecting relapse" (see page 20, 2nd full paragraph of the Remarks filed 1/9/2007; emphasis added). Applicant further argues that '[V]alues for gene expression profiling for patient vs. normal control may vary either up, as in the case of IL 8, or down, as in the case of PPAR-γ. It is the determination of the collective shift for the patient vs. normal control that is significant when using a panel of biomarkers' (see page 20 of the Remarks filed 1/9/2007, as well as the specification at page 8, paragraph 27). Applicant further argues that Figure 2a teaches 6 biomarker genes examined in the mouse MIN model of colon polyps (SDF-1, COX2, CXCR2, OPN, MCSF1 and PPAR-γ) and that Figure 2b shows that 6 correlative human biomarker genes show "similar expression differences" (see page 21, 1st paragraph of the Remarks filed 1/9/2007). Applicant

further argues that a MANOVA analysis of a panel of 9 biomarkers shown in Figure 2c demonstrates a "significant difference in the combined expression of the biomarkers between the normal patient biopsies and the biopsies of non-cancerous sections (ibid). Applicant argues that armed with such teachings regarding the changes in gene expression profiles between CRC patients and validated normal controls and the long history of using biomarkers for the management of patient care, the skilled artisan would know how to use the claimed invention. Applicant further argues that a disclosure need not teach every operable species of the invention. Applicant further argues that while Examiner has cited Barrier et al for support that the state of the art at the time of Applicant's filing was underdeveloped, Barrier et al have since published and shown that stage II cancers are predictable using genetic markers and using techniques that are similar to those cited by Examiner to demonstrate the immaturity in the art. Applicant further argues that "the specification teaches correlating differences of gene expression level of normal appearing mucosa from colon cancer patients to validated normal controls, thus demonstrating that such a method in fact works" (see page 22, 2nd paragraph of the Remarks filed 1/9/2007). Moreover, Applicant argues, claim 57 has been amended to reflect that the difference comprise an

increase in at least one cDNA level in the sample relative to the control (ibid).

Applicant's arguments have been carefully considered but are respectfully found unpersuasive. While examples may be found in the prior art wherein gene expression profiling has been performed to manage patient care, Applicant has not demonstrated that the state of art at the time of filing was developed in such a way as to support the enablement of Applicant's instant claims. Furthermore, while Barrier et al may have published in 2006 that gene expression profiling was capable of predicting the prognosis of stage II colon cancer patients, post-filing art is not germane to the state of the art *at the time of Applicant's filing*. Examiner wishes to clarify and emphasize that Examiner's use of post-filing art (Barrier et al. *Oncogene* **24**:6155-6164, 2005, of record; and Hao et al. *Clinical Cancer Research* 11:1400-1407, 2005, of record) provides support for the assertion that *even post-filing*, the state of the art was underdeveloped both with respect to the use of nucleic acids to diagnose and manage disorders in general, as well as with respect to the use of nucleic acids for the management of patient care and discovery of therapeutic interventions for CRC and colorectal polyps in particular. Furthermore, Applicant's arguments run contrary to the teaching

in the specification that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (see page 5, paragraph 16). Given that state of the prior art was underdeveloped at the time of Applicant's filing, one of ordinary skill in the art would have relied to a larger extent upon the information disclosed in Applicant's specification. Here Applicant's arguments are also found unpersuasive because, while Applicant points to support in the specification to show that differences in gene expression were observed for panels of biomarkers in the context of normal and diseased tissue in both a mouse MIN model of colorectal polyps and in human specimens, the biomarker panels are not comprised of the same biomarkers recited in the claims. Specifically, Applicant's claim 49 is drawn to the use of any two biomarkers from the group comprising SEQ ID NOs: 1, 2 and 5 which encode IL-8, PTGS-2(COX2) and SAA1, respectively. The panel of 6 biomarkers examined in the MIN mouse model and presented in Figure 2a are SDF-1, COX2, CXCR2, OPN, MCSF1 and PPAR-δ. Furthermore, the panel in Figure 2a does not show expression for PPAR-γ (increased, decreased or otherwise), as Applicant asserts. The panel of 6 "correlative human biomarker genes" taught in Figure 2b includes IL-8 and COX2, but not SAA1. The panel of 9 biomarkers analyzed by

MANOVA and present in Figure 2c also does not include SAA1. The instant claims are further drawn to a biomarker panel that includes at least one biomarker from the group comprising PPAR-α or PPAR-γ. However, PPAR-α is also not included in any of the Figures and sections of the specification Applicant uses for support in asserting that the instant claims are enabled. The importance of this discrepancy is highlighted by the teachings in the specification and Applicant's arguments: "It is the determination of the collective shift for the patient vs. normal control that is significant when using a panel of biomarkers" (see page 20 of the Remarks filed 1/9/2007, as well as the specification at page 8, paragraph 27; emphasis added). Applicant's argument that amendment of claim 57 limiting the methods to those in which at least one cDNA biomarker in the sample compared to the cDNA level from a validated normal control identifies a subject as a candidate for the management of colorectal cancer and colorectal polyps is not remedial because 1) the amendment comprises new matter, and 2) it does not address the salient issues set forth in the previous action and herein with regard to at least the state of the art, the support provided by the specification, and the amount of experimentation that would be required for one of ordinary skill in the art to perform the instantly claimed method such that any

of Applicant's claimed utilities, i.e., risk assessment, early diagnosis, establishing prognosis, monitoring treatment and detecting relapse, could be achieved.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view

the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Joseph Woitach can be reached at (571) 272-0739.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

July 19, 2007

/Nancy T. Vogel/
Primary Examiner, Art Unit 1636